PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 269.PF	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2004/000868	International filing date *(day/month/year)* 13.01.2004	Priority date *(day/month/year)* 14.01.2003
International Patent Classification (IPC) or national classification and IPC A61K31/675, A61K31/513		
Applicant GILEAD SCIENCES, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.07.2004	03.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Rodriguez-Palmero, M Telephone No. +49 89 2399-7871

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/000868

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-43 as originally filed

   Claims, Numbers

   1-57 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/000868

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-23 with respect to IA

because:

☒ the said international application, or the said claims Nos. 1-23 with respect to IA relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3,8,12-15,31,32,37-40,42-57
	No:	Claims	1,4-7,9-11,16-30,33-36,41
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-57
Industrial applicability (IA)	Yes:	Claims	24-57
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1: Journal of Infectious Diseases, 2002, 186:1844-7.
   D2: Journal of Virology, 12 Jan 2003, 77:1120-30.
   D3: Project Inform Perspective, Jan 2003, 35:4-7.
   D4: Antiviral Research, 1997, 36:91-97.
   D5: WO00/25797, 11 May 2000.
   D6: WO02/08241, 31 Jan 2002.

1.1 Unless indicated, reference is made to the passages indicated in the international search report.

2. **Novelty (Art. 33(2) PCT)**

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 4-7, 9-11, 16-30, 33-36, 41 is not new in the sense of Article 33(2) PCT.

D1 discloses the use of tenofovir disoproxil fumarate (TDF) in patients receiving lamivudine (3TC) or emtricitabine (FTC) (see page 1844, column 2, second last paragraph). Although this document relates mainly to the treatment of the hepatitis B in HIV/HBV co-infected patients, it also reports that there was an anti-HIV activity (see page 1845, column 2, last paragraph before "Discussion").

D2 shows studies on the appearance of resistances in SIV when using tenofovir (PMPA) with 3TC or PMPA with FTC (see the passages mentioned in the search report).

D3 discloses that there is the intention of combining PMPA with FTC in a single pill (see page 7, column 2, last paragraph).

D4 teaches that the combination of PMPA or adefovir (PMEA) with 3TC induces an additive inhibition of the HIV replication in vitro.

D5 discloses the combination of FTC with PMEA for the treatment of hepatitis B.

Therefore, taking into account that PMPA and PMEA are mentioned in the description of the present patent application to be functional derivatives of GS-7340 (see page 12, lines 4-8), the subject-matter of present claims 1, 4-7, 9-11, 16-30, 33-36 and 41 cannot be considered novel in the light of D1-D5.

2.2 It should be noted that the term "physiological functional derivative" used in independent claims 1, 9 and 24 is considered not to be clear, contrary to Art. 6 PCT. The person skilled in the art does not know which compounds fall in such a definition, apart from those mentioned in the description on page 12, lines 4-19 and page 14, line 12 - page 15, line 25.

3. **Inventive Step (Art. 33(3) PCT)**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-57 does not involve an inventive step in the sense of Article 33(3) PCT.

3.1 Claims 1, 4-7, 9-11, 16-30, 33-36 and 41 are not novel and therefore cannot be considered inventive.

3.2 Claims 2, 3, 8, 12-15, 31, 32, 37-40, 42-57 concern the use of GS-7340 in combination with emtricitabine or a physiological functional derivative thereof.

As mentioned under item 2.1, D1-D4 all mention the combination of PMPA with emtricitabine (D1-D3) or a physiological functional derivative thereof (3TC; see

D4). D1 shows the anti-HIV activity of this combination in vivo, whereas D4 does it in vitro. D2 discloses the use of said combination against the simian immunodeficiency virus, as a model of the HIV infection. D3 also discloses the combination for anti-HIV. These documents are regarded as being the closest prior art to the subject-matter of claims 2, 3, 8, 12-15, 31, 32, 37-40, 42-57.

The subject-matter of said claims therefore differs from D1-D4 in that GS-7340 is used instead of PMPA in combination with 3TC or a physiological functional derivative thereof for the treatment of HIV infections.

The problem to be solved by the present invention may therefore be regarded as which improved combination would be used by the person skilled in the art.

The solution proposed in said claims of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
D6 teaches that GS-7340 is a prodrug of tenofovir which shows more potent anti-HIV activity than tenofovir in vitro. Moreover, this document also discloses that GS-7340 has a higher plasma stability than tenofovir, which is expected to result in higher circulating levels of GS-7340 than TDF after oral administration.

Therefore, the person skilled in the art willing to improve the combinations already known from D1-D4 and considering the teachings of D6 would be prompted to replace TDF by GS-7340.

3.3 The Applicant is asked to note that present application lacks technical data showing that the problem posed by the present application is solved.

4. Industrial applicability (Art. 33(4) PCT)

4.1 For the assessment of the present claims 1-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4.2 Present claims 24-57 are susceptible of industrial application and thus do not contravene Art. 33(4) PCT.